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ZISKA, S — EXAMINER

18M2/0623

MORRISON & FOERSTER
2000 PENN. AVE. N.W.
WASHINGTON, D.C. 20006-1812

ART UNIT	PAPER NUMBER
1804	11

1804

DATE MAILED: 06/23/94

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 5/9/94 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire three (3) month(s), zero (0) days from the date of this letter. Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☒ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☒ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☒ Claims 54, 35, 36-39, 68, 69, 82, 16-26, 75-78, 79-81 are pending in the application.
   Of the above, claims 34-39, 68, 69 and 82 are withdrawn from consideration.
2. ☒ Claims 1-15, 27-33, 46-67, 70-74 have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 16-26, 75-78, 79-81 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____, has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

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PTOL-326 (Rev. 2/93)

EXAMINER'S ACTION

This application should be reviewed for errors.

Applicant's election without traverse of Groups I-III,V and VII-XI in Paper No. 8 is acknowledged. Applicant's election with traverse of Group IV, claims 16-26 and 75-78 in Paper No. 8 is acknowledged. The traversal is on the ground(s) that the claims of Groups IV and Group VI have the same classification (Class 800, subclass 2, for example) therefore searching the inventions of the two groups should not be burdensome. This is not found persuasive because the although the classification is the same, the search of Group IV, for example, does not required a search of homologous recombination using YACs, which is the search required by Group VI. As previously stated, restriction is proper in view of the recognized divergent subject matter and separate search requirements.

The requirement is still deemed proper and is therefore made FINAL.

Applicants have added new claims 79-82. Claims 79-81 are drawn to a genetically modified nonhuman animal having a genetic modification resulting in the inability of said animal to produce endogenous antibodies in response to an antigenic challenge and wherein said genetic modification permits production of non-endogenous antibodies in response to an antigenic challenge whereas claim 82 is drawn to a non-human animal modified to contain a YAC construct in addition to being further modified so as to be incapable of producing endogenous antibodies. The search of claim 82 is different than the search of claims 79-81 and claim 82 is assigned to Invention VI (claims 34-39, 68 and 69), which for reasons as stated above, has been withdrawn from consideration. Claims 79-81 are assigned to Group IV, claims 16-26 and 75-78, drawn to a genetically modified non-human animal having a modified genome, not using YACs, classified in Class 800, subclass 2, for example.

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Claims 1-15, 27-33, 40-67 and 70-74 have been cancelled; claims 79-82 have been newly added; claims 16-26, 75-78 and 79-81 are examined in this Office Action.

Claims 16-18, 21-26, 75-81 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase "...inability of at least one locus to produce...." is vague and unclear since the basis of the inability is indefinite and may be due to variety of reasons known to those skilled in the art such as rearrangement of the genes and not due to homologous recombination, for example. Further, in claim 16 and others having the phrase "...one locus to produce endogenous immunoglobulin heavy and light chains" is vague and unclear since the heavy and light chain genes are produced from diffent loci and the knockout of one loci does not include the knock out of the other.

Regarding claims 21, 22 and 25, the phrase "and/or" is vague and unclear since the term renders the claim indefinite.

Regarding claims 79-81, claim 79 is vague and unclear since the "genetic modification" referred to in line 2 refers to the knock out of the endogenous gene and the second occurrence of "genetic modification" refers to the insertion of xenogeneic immunoglobulin genes. Note that "said genetic modification" cannot correctly refer in the first case to the knock out of the endogenous gene and in the second case, the insertion of the xenogeneic immunoglobulin genes.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention."

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The specification is objected to under 35 U.S.C. 112, first paragraph, as failing to provide an adequate written description of the invention and for failing to adequately teach how to make and/or use the invention as claimed, i.e., failing to provide an enabling disclosure. Regarding claims 16, 18-26, 75-80, Applicants have disclosed a genetically modified mouse comprising a genome modified to contain human immunoglobulin genes and have failed to disclose any other non-human animal so modified. In view of the complexities of the design of the gene inactivation (targeting) vector and the requirement of nucleotide sequence knowledge needed to assure homologous recombination into the desired site, claims 16, 18-26, 75-80 must be limited to mice since the nucleotide sequence of the immunoglobulin genes of other non-human animals is not available in the prior art. It would required undue experimentation of one of ordinary skill to create the body of sequences needed to practice the invention with other non-human animals. NOte that both terms "rodents" and "murine" do not specify mice. "Murine" may be rats and "rodents" include other animals such as hamsters and gerbils.

In addition, claims 16-26, 75-81 must be limited to the J region or the kappa constant region since the specification fails to provide guidance to one of ordinary skill to modify the V region in a similar manner.

Regarding claims 79-81, the specification fails to provide evidence that the genetically modified mouse having the J region or Ck region knocked out and a xenogeneic immunoglobulin gene inserted would produce xenogeneic antibodies in response to an antigenic challenge. Note that it is well known in the art that VH regions exist on more than one chromosome and that those Vh regions are used in the antigenic response. Applicants have not knocked out the endogenous Vh regions and there are teachings in the art which suggest that Vh regions from other chromosomes may be used (Matsuda, Nature *genetics*). There is no evidence presented in the specification that, without knocking out the endogenous Vh regions, that the

antibody so produced would be purely xenogeneic in nature. In addition, it is known in the art that unmutated germ-line Vh genes encode autoantibodies. Thus, without knockout of the Vh region, the mouse may produce autoantibodies, which are antibodies produced to the mouse tissue and not produce antibodies to the injected antigen (Shin et al.). In view of the known species differences between mice and men, and the vagaries of eliciting immune responses, and the lack of evidence to support the claimed invention, the specification is not enabling for the production of antibodies using the xenogeneic immunoglobulin genes.

Claims 16-26, 75-81 are rejected under 35 U.S.C. 112, first paragraph, for the reasons set forth in the objection to the specification.

The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103.

Claims 16-26 and 75-81 are rejected under 35 U.S.C. 103 as being unpatentable over Bruggemann (PNAS, 1989) taken with any of Joyner et al., Thomas et al., and Koller et al. and further in view of Fell (U.S.P.N. 5,204,244). Bruggemann discloses transgenic mice having human immunoglobulin genes introduced in their unrearranged configuration into the germ line. Bruggemann further discloses a human heavy chain minilocus comprising unrearranged immunoglobulin variable, diversity and joining elements linked to a human mu chain gene. Bruggemann discloses that the gene segments of the minilocus are rearranged in a large proportion of cells in thymus or spleen but not in nonlymphoid tissue. Bruggemann discloses that B lymphocytes synthesize human mu chains resulting in the production of transgenic IgM in the serum of the mouse. Bruggemann differs from the claims in that the reference fails to disclose a genome which has a modification resulting in the inability to produce endogenous immunoglobulin heavy or light chains. However, the secondary references, Joyner, Thomas and Koller cure the deficiency. Thomas discloses gene targeting in mouse embryo-derived stem cells by homologous recombination and that the procedure used should be useful for targeting mutations into any gene. Joyner discloses gene targeting of the *En-2* gene in mouse embryonic stem cells by homologous recombination. Koller discloses inactivation of the beta-2-microglobulin locus in mouse embryonic stem cells by homologous recombination and the production of chimeric mice from those murine embryonic stem cells. Collectively the secondary references Joyner, Thomas and Koller teach genetic modification of a desired gene in mouse embryonic stem cells (ES cells), that the ES cells thus obtained can produce transgenic mice carrying the genetic modification and that the genetic modification is obtained in the germline and thus the genetic modification is transmissible to offspring. Fell discloses the use of homologous recombination to replace the J region or the J region and the

kappa constant region in lymphocytes. Fell is thus cited to disclose that immunoglobulin genes can be successful altered by gene targeting using homologous recombination.

It would have been obvious to one of ordinary skill to modify the mouse of Bruggemann by gene targeting using homologous recombination to knock-out (inactivate) an immunoglobulin gene containing region in view of the teachings of Bruggemann. Bruggemann provides the motivation to combine the references on page 6712, last paragraph, wherein it is stated "It would be useful to have transgenic mice that have nonfunctional endogenous immunoglobulin gene loci so that they can only make human antibodies".

Regarding the production of xenogeneic light chains, the homologous recombination techniques would be the same and Fell discloses that either the light chain or heavy chain genes can be altered (column 9, lines 30-68 and column 10, lines 1-33).

Regarding claim 17, Joyner, Thomas, Fell, Bruggemann all disclose use of mice.

Regarding claim 18, Bruggemann discloses that the xenogeneic immunoglobulin is human.

Regarding claim 19, Joyner, Thomas, and Koller disclose inactivation of the desired gene via homologous recombination as does Fell.

Regarding claim 20, Fell discloses replacement of murine sequences by human sequences via homologous recombination for purposes of producing xenogeneic immunoglobulins.

Regarding claims 21-26, Fell discloses replacement of the murine immunoglobulin genes with human immunoglobulin genes via gene targeting and Koller discloses inactivation of the beta-2-microglobulin gene via gene targeting and homologous recombination with a construct containing a Neo

gene which effectively causes a lesion in the gene and results in the beta-2-microglobulin locus being incapable of expressing the beta-2-microglobulin protein. Therefore, the combination of references renders obvious the claimed invention.

Regarding claims 75-78, Koller discloses that breeding the mice having the genetically modified genome would allow the investigation of the effects of the homozygous state. It would have been obvious to one of ordinary skill to obtain genetically modified animals being either heterozygous or homozygous for endogenous gene knockout and heterozygous or homozygous for xenogeneic immunoglobulin expression in view of the teachings of Koller that breeding of genetically modified animals is used to obtain homozygous expression of traits. In addition, such techniques are well known to those of ordinary skill since the days of Mendel and the cross-breeding experiments using peas.

Regarding claims 79-81, Bruggemann discloses that transgenic mice containing human immunoglobulin genes would not be tolerant to most human determinants and could be used to make human antibodies against human antigens (page 6712, column 1 top paragraph). Therefore Bruggemann inherently suggests an antigenic challenge of such mice to produce human antibodies against human antigens.

Accordingly, the modification of mouse of Bruggemann by altering the genome to knock-out the endogenous immunoglobulin genes as suggested by Joyner, Thomas, Koller and Fell in order to obtain a mouse having a genome heterozygous for a modification that results in the inability of at least one locus to produce endogenous immunoglobulin heavy or light chains and hemizygous for a modification that results in the ability to produce xenogeneic immunoglobulin heavy and light chains was within the ordinary skill in the art at the time the claimed invention was made. From the teachings of the references, it is apparent that one of ordinary skill would have had a reasonable expectation of success in producing the claimed

invention. Therefore, the invention as a whole is prima facie obvious, as evidenced by the references, especially in the absence of evidence to the contrary.

No claim is allowed.

Papers related to this application may be submitted to Group 180 by facsimile transmission. Papers should be faxed to Group 180 via the PTO Fax center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703)308-4227.

An inquiry concerning this communication or earlier communications from the Examiner should be directed to Examiner Suzanne Ziska, Ph.D., at telephone number 703-308-1217. The Examiner can normally be reached on Monday through Friday from 8:00 AM to 4:30 PM.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ms. Elizabeth Weimar, can be reached on (703) 308-0254.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Suzanne Ziska

SUZANNE E. ZISKA
PRIMARY EXAMINER
GROUP 1800
6/22/94

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